Endocrine disorders and their impact on reproductive health: modern aspects of diagnosis and treatment

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Abstract
This work is a comprehensive review of modern aspects of the diagnosis and treatment of endocrine disorders and their impact on reproductive health. The basic principles of the functioning of the human endocrine system are highlighted, including the role of hormonal balance in maintaining the health and functioning of the reproductive system. Various types of endocrine disorders and their effects on reproductive health are also being investigated. In particular, conditions such as hypothyroidism, hyperthyroidism, polycystic ovary syndrome (PCOS), hyperprolactinemia and diabetes, their symptoms, diagnosis and treatment are highlighted. Special attention is paid to the relationship between endocrine disorders and infertility, as well as methods of correcting hormonal imbalances to restore reproductive function.

In addition, modern methods of diagnosis and treatment of endocrine disorders are discussed, including laboratory and instrumental methods, molecular genetic studies, as well as advanced approaches in pharmacological therapy, surgical interventions and alternative methods such as active surveillance and lifestyle changes.

Keywords
Endocrine disorders, Reproductive health, Diagnosis, Treatment.

INTRODUCTION

Infertility rates are on the rise all over the world. Medical professionals have to cope with reproductive difficulties caused by endocrinological changes or disorders, delayed childbirth, negative environmental influences, as well as lifestyle and nutrition changes. The prevalence of infertility has increased significantly in recent decades, affecting 8-12% of couples of reproductive age [1].

Endocrine disorders represent a wide range of conditions associated with impaired functioning of the endocrine system, which plays a key role in maintaining homeostasis and regulating many important processes in the human body. One of the most significant aspects affected by endocrine disorders is reproductive health.

The human reproductive system is closely related to the endocrine system, and any disorders in the latter can have a significant impact on the function of reproductive organs and processes. Endocrine disorders can lead to menstrual irregularities in women, infertility, decreased libido and erectile function in men, as well as other reproductive health problems [2].

Among women of reproductive age, hypothyroidism is a common cause of infertility due to anovulation with a prevalence of 3-5%. Worldwide, the prevalence of Hashimoto’s thyroiditis, which increases with age, currently ranges from 8 to 14% among women of reproductive age, and the frequency of autoimmune thyroid diseases (AITD) even higher among infertile women. According to the patient registers of assisted reproduction centers, the frequency of thyroid autoimmunity (TAI) can reach 20%

In the light of the rapid development of modern medicine and biological sciences, including endocrinology and reproductive medicine, there is a need for constant updating of knowledge about the mechanisms of occurrence, diagnosis and treatment of endocrine disorders, as well as their impact on reproductive health.

In this article, we will review modern aspects of the diagnosis and treatment of endocrine disorders and their impact on reproductive health. We will consider the main endocrine systems, the mechanisms of the
influence of endocrine disorders on the reproductive system, modern methods of diagnosis and treatment of endocrine disorders, as well as prospects and directions for further research in this area.

Understanding these aspects is key to developing effective strategies for the prevention, diagnosis and treatment of endocrine disorders aimed at maintaining and restoring reproductive health in men and women.

MATERIALS AND METHODS

In the process of writing the work, an extensive analysis of the scientific literature was carried out to assess existing theoretical concepts, mechanisms of hormone action and pathophysiology of endocrine disorders, as well as their impact on the reproductive system. The relationship between various factors, including hormone levels, the functional state of organs and systems, and reproductive health, was examined. The features of the application of biological data analysis methods to identify the molecular mechanisms of hormone action, identify genetic associations with endocrine disorders and assess their impact on reproductive function are also considered. Theoretical hypotheses about the pathogenesis of endocrine disorders and their consequences for reproductive health are analyzed using logical reasoning and data analysis, and conceptual models describing the interaction between various components of the endocrine system and reproductive function, as well as identifying key points of impact for diagnosis and treatment, are investigated. The use of these methods allows for an in-depth understanding of the mechanisms of development of endocrine disorders, their impact on reproductive health, as well as to develop new strategies for the diagnosis, treatment and prevention of these conditions.

RESULTS

Thyroid diseases affect almost 14% of adult women and are among the most common endocrinopathies in women of reproductive age [3]. There is an assumption in the literature that the female sex seems to be an independent risk factor for thyroid dysfunction, since women are 3-5 times more likely to be treated for thyroid diseases than men. Similarly, higher chances of thyroid disease have been reported in overweight people. Unfortunately, many thyroid diseases are associated with adverse effects on reproductive and metabolic health. For example, subclinical hypothyroidism (SH) is associated with polycystic ovary syndrome (PCOS), a reproductive disorder characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovary morphology. In women with PCOS, hypothyroidism is associated with concomitant diseases such as dyslipidemia and insulin resistance. Among women with autoimmune thyroid diseases such as Graves' disease or Hashimoto's thyroiditis, the infertility rate is approaching 50%, along with a higher prevalence of premature ovarian failure.

Thyroid diseases affect the reproductive function of women in a pleiotropic way, having both direct and indirect effects on various levels of the female reproductive axis [4]. At the hypothalamic-pituitary level, thyroid hormones (TH) regulate the secretion of kisspeptin and gonadotropin-releasing hormone (GtRH) both directly and through metabolic signals such as prolactin and leptin. In addition, TH affects the bioavailability of sex steroids through changes in binding proteins. The euthyroid status promotes the functioning and development of the normal female reproductive tract and regulates the development of the placenta and fetus during pregnancy.

The complex interaction of the thyroid gland and female reproduction deserves a comprehensive review to identify the nuances affecting the clinical treatment of thyroid and reproductive system disorders [5].

Given the closely interrelated role of TH with reproductive physiology, it is not surprising that thyroid-related dysfunction is more common in various reproductive pathologies, including subfertility, PCOS and endometrial dysfunction. Violation of hypothalamic secretion of kisspeptin, GnRH and gonadotropins is associated with thyroid dysfunction in the form of TH. In one study, LH and FSH levels were suppressed in women with hypothyroidism and increased in response to achieving euthyroid status. It is assumed that these effects are the result of a decrease in hypothalamic secretion of kisspeptin and GtRH [6].

The adverse effects of thyroid-related diseases on ovarian function are well documented, and negative effects on fertility are also observed. A recent systematic review examined anti-muller hormone (AMH), a widely used quantitative marker of ovarian reserve, in participants in several studies and found significantly lower levels of AMH in women with autoimmune thyroid disease (AITD) without distinction between
euthyroid and hypothyroid individuals. This observed association between AITD and a decrease in ovarian reserve has been replicated in several other studies [7]. However, both studies found no significant association between reproductive outcomes and TSH levels. These effects can be explained by a common autoimmune etiology, since both Hashimoto’s thyroiditis and Graves’ disease are autoimmune-mediated hypothyroid and hyperthyroid conditions, respectively, and both are associated with high rates of infertility (47% and 52%, respectively).

Premature ovarian insufficiency (POI) is characterized by the cessation of ovarian function before the age of 40 years. As in the case of reduced ovarian reserve, autoimmunity explains the phenotypes of the thyroid gland and reproductive system in POI, at least in some women with POI [8]. For example, several studies have identified a link between POI and thyroid-related autoimmunity. These data provide additional evidence for the hypothesis that autoimmune diseases of the thyroid gland and ovaries share an autoimmune relationship, which is especially relevant for Graves’ disease and Hashimoto’s thyroiditis, both of which are associated with POI symptoms. Autoimmunity is manifested in autoimmune polyglandular syndromes (APS), in which the prevalence of autoimmune damage to endocrine organs is high, including PNH (up to 50%) and autoimmune thyroid diseases (up to 70%) [9].

Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disease in women of childbearing age, affecting 3-15% of women worldwide. PCOS causes reproductive disorders, metabolic disorders and psychological problems that can seriously affect the physical and mental health of these women.

PCOS is a very clinically heterogeneous disease. There are four specific phenotypes that vary greatly depending on the stage of life, genotype, race, and environmental factors. The four PCOS phenotypes are classified according to three factors: polycystic ovarian morphology, ovulation dysfunction, and hyperandrogenemia. The etiology and pathogenesis of PCOS remain unclear, primarily due to the heterogeneity of these phenotypes, which increases the difficulty of treating this complex endocrine disease [10].

The clinical manifestations of PCOS are similar to some thyroid diseases. There is increasing evidence that PCOS is associated with an increase in the incidence of thyroid diseases such as autoimmune thyroiditis (AIT) and subclinical hypothyroidism (SH).

The severity of metabolic disorders in PCOS patients is associated with the degree of thyroid dysfunction. If the level of thyroid hormones is too high, hyperthyroidism will appear, accompanied by symptoms such as overeating, hunger and exhaustion [11]. Conversely, if the level of thyroid hormones is too low, hypothyroidism occurs.

Recent studies have shown that the incidence of hypothyroidism is higher in patients diagnosed with PCOS (11-14%) compared with the control group (1-2%). Metabolic changes observed in both hypothyroidism and PCOS include insulin resistance, dyslipidemia, weight gain, and obesity. Compared with patients with PCOS with normal thyroid function, women with PCOS and CHF have higher triglyceride levels, fasting insulin levels and HOMA-IR [12]. In addition, hypothyroidism often occurs in patients with GB. Patients with combined PCOS and GT had more severe metabolic symptoms than patients with PCOS or GT alone. Women with combined GT and PCOS had a higher BMI, fasting blood glucose, HOMA-IR, and cholesterol compared to the control group or the GT-only group. These data suggest that the combination of PCOS and hypothyroidism is associated with more significant metabolic and hormonal changes.

Metabolic disorders in PCOS patients with subclinical and clinical hypothyroidism associated with GT significantly improved when taking thyroid supplements compared to patients with normal thyroid function, which provides additional evidence that the metabolic disorders observed in PCOS patients are associated with thyroid dysfunction. They improve after thyroid function is normalized [13].

Polycystic ovary syndrome (PCOS) is characterized by a combination of hyperandrogenism, ovulatory dysfunction and polycystic ovaries and is associated with abnormal thyroid status. In addition, PCOS and hypothyroidism have common risks and common manifestations, such as oligomenorrhea, infertility, insulin resistance and dyslipidemia, which requires a thorough endocrine examination of patients with these features. It is important to note that hypothyroidism is also associated with poor prognostic indicators of PCOS.

In addition to its role in hypothalamic, pituitary, and ovarian dysfunction, TG-related dysfunction is associated with a variety of uterine and endometrial disorders, including endometriosis, infertility, and dys-
functional uterine bleeding. For example, it has been reported that AITD contributes to the complex pathophysiology of endometriosis. Menstrual dysfunction is perhaps the most clearly related endometrial symptom associated with thyroid dysfunction. In general, hypothyroidism was found to be associated with profuse bleeding and polymenorrhea, and hyperthyroidism with oligomenorrhea and amenorrhea [14]. While earlier studies documented a significant association between thyroid dysfunction and menstrual disorders, recent studies have found significant differences in menstrual disorders only in the case of severe thyroid disease, possibly due to earlier diagnosis and treatment of thyroid diseases in the modern era.

Given the increased demands of pregnancy on the mother's thyroid system, current recommendations suggest that women should be carefully screened for thyroid dysfunction throughout pregnancy. Several factors appear to mediate adverse thyroid-related outcomes, including AITD (high TPO antibodies), low HCG levels, insufficient iodine intake, BMI, and the status of subclinical hypothyroidism [15]. It is well known that overt hypothyroidism poses serious risks to the mother and fetus, including placental abruption, postpartum bleeding and severe premature birth. Although the risks and benefits of treating subclinical hypothyroidism (SH) are controversial, SH itself also appears to be associated with adverse pregnancy outcomes such as preeclampsia and premature birth.

Hyperthyroidism during pregnancy can manifest itself in both an obvious clinical and mild subclinical form and is observed in about 0.2% of pregnancies. Overt hyperthyroidism is usually defined as TSH suppression with an increase in TG levels exceeding the trimester-specific ranges or more than 1.5 times the reference range for non-pregnant women, and, like hypothyroidism, can mediate adverse outcomes such as preeclampsia, placenta previa and premature birth [16]. It is usually found against the background of Graves’ disease and HCG-mediated forms, such as hyperemesis of pregnant women and gestational transient thyrotoxicosis (GTT). Although Graves’ disease improves over time by reducing antibody titers, HCG-mediated forms vary depending on the etiology. While HCG levels peak at the end of the first trimester, GTT and hyperemesis of pregnant women (HM) may worsen and then decrease. In most cases, HM requires supportive treatment, but rarely requires termination of pregnancy [17].

Overt hyperthyroidism is the most serious problem for clinicians due to the increased likelihood of side effects such as hospitalization in the intensive care unit, venous thromboembolism and premature rupture of the membranes [18]. On the contrary, milder and benign forms of HCG-mediated hyperthyroidism may be clinically unnoticeable and manifest as subclinical hyperthyroidism characterized by TSH suppression and an increase in T3 and/or T4 levels <1.5 times higher than the upper limit of normal. An increase in TG levels may occur physiologically in 3% of women due to a sharp increase in HCG levels during pregnancy, and in women with multiple pregnancies this increase may be quite high.

DISCUSSION

The goal of therapy in non-pregnant women is to restore clinical and biochemical euthyroidism, which will also improve any concomitant reproductive dysfunction (oligomenorrhea, amenorrhea, infertility, hyperprolactinemia, etc.). With age, target TSH levels continue to shift upwards [19]. Hypothyroidism in non-pregnant women is treated with LT4 hormone replacement therapy. Given the approximate half-life of LT4, which is one week, it is important to ensure sufficient duration of treatment to measure thyroid function tests. In the vast majority of women, only LT4 therapy at a dose of 1.6–1.8 micrograms/kg of body weight is sufficient to completely replace endogenous thyroid function [20]. Women planning to conceive should have a target TSH level before conception between the lower reference range and 2.5 μme/L, and LT4 doses should be adjusted accordingly.

Finally, thyroxine-binding globulin levels may be higher in women receiving estradiol replacement therapy or contraception, which makes existing doses of thyroid replacement therapy insufficient. A reasonable approach may be to conduct thyroid functional tests 6-12 weeks after starting estrogen supplementation or contraception, especially in pre-existing hypoestrogenic conditions. Moreover, in conditions associated with elevated thyroxine-binding globulin levels, it is recommended to rely on the level of free T4 rather than on the total T4 level (which may be increased) when adjusting the dose and making a treatment decision [21].

In perimenopausal and postmenopausal women, the manifestations and treatment of hypothyroidism are somewhat different from those in premenopausal
majority of thyroid nodules are benign, but those with suspected malignant neoplasm are usually referred for thyroidectomy. Thyroidectomy, if indicated, is ideally performed six months before conception to minimize the risk of infection of the fetus with maternal hypothyroidism.

It is also necessary to consider the specifics of the treatment of endocrine pathologies in pregnant women. Although the goals of treating hypothyroidism in pregnant women are almost identical to the goals of treating non-pregnant mothers, clinicians face certain problems [26]. Firstly, the symptoms of hypothyroidism and pregnancy are largely the same (e.g. weight gain, fatigue, constipation, etc.), which makes the diagnosis of hypothyroidism in pregnant women clinically challenging and can lead to delays in diagnosis. Secondly, there are differences of opinion regarding the treatment of women with abnormal TSH and sT4 without previously diagnosed hypothyroidism. Thirdly, physiological changes in thyroid homeostasis occur in each trimester, and treatment must be adapted to each trimester. Fourth, some fT4 immunoassays become unreliable, which requires repeated testing of abnormal values using another (more reliable) analysis and compliance with trimester-specific thyroid function values [27].

It is important to note that improper treatment of hypothyroidism can have serious consequences for pregnancy outcomes (for example, premature birth, low fetal weight, postpartum bleeding, etc.) and the fetus (neurocognitive disorders, perinatal mortality, etc.) [28].

Pregnant women are recommended to maintain TSH levels within the lower reference limit and 2.5 mEd/L in the first trimester. Against the background of this increase, thyroid functional tests should be performed every 4-6 weeks with titration of the dose to achieve the target TSH level, depending on the trimester or TSH level below 2.5 mEd/L. After childbirth, LT4 doses should be reduced to the level that was before pregnancy, and thyroid function should be assessed after four to six weeks [29]. It is also necessary to remember about the decrease in the absorption of LT4 when used simultaneously with drugs commonly used during pregnancy, such as omeprazole and iron preparations. Patients should be reminded to observe the appropriate time interval between meals.

The most common causes of hyperthyroidism during pregnancy are gestational transient thyrotoxicosis (GTT) and Graves’ disease [30]. The distinction
between the two is crucial and requires careful medical history, physical examination, and appropriate laboratory tests. For example, the absence of goiter and orbitopathy, as well as the presence of severe vomiting symptoms, make it possible to diagnose GTT compared to Graves’ disease. GTT also tends to be accompanied by higher HCG levels than Graves’ disease. Etiologies such as single nodules and gestational trophoblastic disease are less common.

Doctors should base their decision on whether to treat newly diagnosed hyperthyroidism in pregnant women based on clinical features, thyroid tests and TRAb status [31]. Situations that usually do not require antithyroid drug therapy include transient subclinical hyperthyroidism (low TSH, but normal T4, T3), GTT, which usually resolves on its own, hyperemesis of pregnant women without obvious hyperthyroidism (maintenance therapy is required), mild Graves’ disease or subclinical hyperthyroidism of any etiology (T3 and T4 < 1.5 times higher the upper reference boundary).

The goals of treatment are determined by the physiology of a normal pregnancy. For example, during the first trimester, there is an increased need for T4 for proper maternal and fetal health, and thus target TG levels are lowered to ensure increased T4 delivery. If a pregnant patient is already taking a low dose of thionamide (less than 5-10 mg/day of methimazole or less than 100-200 mg/day of PTU), trial pharmacotherapy may be justified based on recent thyroid functional tests, TRAb levels, and treatment anamnesis and goiter size, in order to maintain T4 levels <1.5 times higher than the upper control limit. If antithyroid drug therapy is discontinued, thyroid function testing should be performed every one to two weeks until a stable level is reached, after which thyroid function tests can be performed intermittently [32].

According to experts, fine needle aspiration of thyroid nodes is safe during pregnancy, but can be postponed until the postpartum period if there are no serious alarm signals, such as lymphadenopathy or extrathyroid spread. In rare cases, if suspicious thyroid nodules require urgent treatment, the optimal time for thyroid surgery is the second trimester, but in most cases, final therapy can be postponed until the postpartum period. It is important to note that radioactive iodine should be avoided both during and for at least 4 weeks after stopping breastfeeding due to its ability to accumulate in the breast.

CONCLUSIONS

Endocrine disorders can have a significant impact on reproductive health in both men and women. Modern aspects of the diagnosis and treatment of these disorders play an important role in maintaining and restoring reproductive function. Hormonal balance plays a key role in the regulation of reproductive function in men and women. An imbalance of hormones can lead to various disorders in the reproductive system. Examples of such disorders are polycystic ovary syndrome (PCOS), hyperprolactinemia, hypothyroidism and hyperthyroidism. These conditions can lead to anovulation, infertility, menstrual irregularities and other reproductive health problems.

Disorders such as hypogonadism and hyperprolactinemia can affect sperm quality and genital gland function, which can lead to decreased fertility and infertility. The use of modern diagnostic methods, such as measuring the level of hormones in the blood, ultrasound and molecular genetic analyses, allows you to accurately determine the presence of endocrine disorders and their impact on reproductive health.

An individual approach to treatment, including hormonal balance correction, drug therapy, surgery and rehabilitation measures, allows effective restoration of reproductive function in endocrine disorders.

The role of the thyroid gland in reproductive function is complex and includes many features. Thyroid dysfunction directly affects the clinical manifestations of various reproductive-related pathologies. Various clinical data strongly suggest that the thyroid gland plays a crucial role in the pathogenesis, development and progression of infertility. Thus, patients planning pregnancy and having a history of endocrine pathologies require careful identification, monitoring and correction of thyroid function over time, which will reduce the risk of miscarriage or the development of various pathologies in the mother or fetus.

Solving reproductive health problems related to endocrine disorders often requires the cooperation of endocrinologists, gynecologists, andrologists, urologists and other specialists to achieve optimal treatment results. In general, understanding modern aspects of the diagnosis and treatment of endocrine disorders is essential for the successful restoration and maintenance of reproductive health in both men and women.
REFERENCES


